ORIGINAL ARTICLE

Anemia is independently associated with NT-proBNP levels in asymptomatic predialysis patients with chronic kidney disease

Tirmenstajn-Jankovic B[1], Dimkovic N[2], Perunicic-Pekovic G[3], Radojicic Z[4], Bastac D[5], Zikic S[1], Zivanovic M[1]

[1]Department of Nephrology and Hemodialysis, Medical Center Zajecar
[2]Clinical Department for Renal Disease, Zvezdara University Medical Center, Belgrade
[3]Department of Nephrology, University Hospital Zemun-Belgrade
[4] Institute for Statistics, Faculty of Organizational Sciences, University of Belgrade
[5]Office of Internal Medicine «Dr Bastac», Zajecar
Serbia

Abstract

Background: Although anemia and renal dysfunction are related to increased natriuretic peptides levels in heart failure patients, less is known about this relationship in asymptomatic predialysis patients with chronic kidney disease (CKD). The aim of this study was to investigate relationship between hemoglobin (Hb) concentration, N-terminal proBNP (NT-proBNP) levels and echocardiographic findings in these patients.

Methods: The study included 61 patients with CKD stage IV-V (34 male, mean age 62.6 ± 13.6 years) and 22 age- and sex -matched healthy persons as control group. All participants underwent clinical, laboratory and echocardiographic examination, including Tissue Doppler Imaging and colour M-mode Doppler.

Results: Patients with CKD had lower Hb levels ($p<0.001$), and higher levels of NT-proBNP ($p<0.001$) than healthy controls. Patients were divided into two groups according to their mean Hb levels: group A, Hb<10.3 g/dL and group B, Hb≥10.3 g/dL. Patients from group A was significantly older ($p<0.001$), left ventricular mass index was significantly higher (LVMI, $p<0.001$), LV diastolic function was worse (septal and lateral E'/A' ratio: $p<0.05$ and $p<0.01$, respectively), and the level NT-proBNP was higher ($p<0.001$) compared to patients from group B. The natural logarithm of NT-proBNP (lnNT-proBNP) showed highly significant correlation with Hb ($p<0.001$) and significant correlation with estimated glomerular filtration rate ($p=0.035$) in CKD patients. Multiple regression analysis revealed Hb levels ($p<0.01$), cholesterol ($p<0.001$), LV ejection fraction ($p<0.001$) and septal E/E' ratio ($p<0.01$) as the independent variables predicting as much as 54% variability of lnNTpro-BNP.

Conclusions: The increased NT-proBNP levels in asymptomatic patients with advanced CKD were independently associated with echocardiographic parameters of LV function, but anemia may represent one of the important confounder of the relationship between NT-proBNP and cardiovascular abnormalities. Hippokratia 2013; 17 (4): 307-312

Key words: NT-proBNP, anemia, left ventricular dysfunction, chronic kidney disease

Corresponding author: Tirmenstajn-Jankovic Biserka, Department of Nephrology and Hemodialysis, General Hospital, Medical Center «Zajecar», Rasadnicka bb, 19000 Zajecar, Serbia, tel +38119445646, fax +38119420672, email: biserkatirmenstajn@gmail.com

Introduction

Anemia occurs early in patients with chronic kidney disease (CKD) and progress relentlessly as renal function declines[1]. Factors likely contributing to anemia in CKD include decreased production of erythropoietin, iron deficiency, blood loss, shortened red cell life span, vitamin deficiencies, accumulation of uremic toxins and inflammation[2]. The tissue hypoxia present in anemia leads to vasodilatation and reduced blood pressure. Thereafter, activation of the sympathetic nervous system and renin-angiotensin-aldosterone system reduces renal blood flow and glomerular filtration rate and increases sodium and water absorption. Combined effects of volume expansion and vasodilatation result in a high cardiac output state[3]. In the long run, increased myocardial workload can lead to unfavorable remodeling of the left ventricle (LV) with LV hypertrophy and dilatation, myocardial cell death, cardiac fibrosis and chronic heart failure[4].

Brain natriuretic peptide (BNP) is a neurohormone predominantly secreted from the cardiac ventricles in response to volume expansion and increased LV wall stress. BNP is synthesized as preproBNP, enzymatically cleaved to proBNP in response to myocite stretch, and subsequently released in circulation as biologically active BNP and inactive N-terminal fragment (NT-proBNP). Recently, these hormones have been extensively studied as useful biochemical markers of heart failure and asymptomatic LV dysfunction in the general population[5]. Both BNP and NT-proBNP have also been shown to be reliable markers of LV hypertrophy, systolic dysfunction, coronary artery disease and LV overload in patients with

different stages of CKD[6-9]. It has been described that both hormones are influenced by several other factors such as age, sex, obesity, renal function and anemia[10]. Although several recent studies has reported an association between anemia and elevated levels of natriuretic peptides in patients with and without heart failure, mechanism of this association is not clearly defined[11-13]. There are fewer studies examining anemia as a potential predictor of BNP/NT-proBNP levels in patients with CKD[10,14].

The aim of this study was to investigate the association between hemoglobin (Hb) level, structural and functional cardiac abnormalities and circulating levels of NT-proBNP in asymptomatic patients with advanced CKD.

Patients and Methods

This cross-sectional study enrolled 61 patients with CKD stage IV-V not yet undergoing renal replacement therapy and 22 age- and sex-matched healthy volunteers as a control group. Patients with CKD were recruited from the outpatient clinic of the Department of Internal Medicine, General Hospital Zajecar, from February 2007 to December 2010. The patient group comprised 34 men and 27 women, mean age 62.6 ± 13.6 years, who did not have clinical evidence of heart failure and/or coronary heart disease. Heart failure was excluded based on absence of heart failure symptoms and physical signs of raised jugular venous pressure or bilateral crepitations on auscultation of the chest. Patients with a known diagnosis of heart failure or coronary heart disease (i.e., patients with angina, use of nitrates and/or a history of myocardial infarction) were also excluded from the study. Thirteen patients were current smokers (20 ± 15 cigarettes/day). A total of 54 patients were on antihypertensive treatment (13 on monotherapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor type I antagonists, calcium channel blockers or β-blockers and 41 on double and triple therapy with various combinations of these drugs). The prevalence of diabetes mellitus in this cohort was 6.5% (4 of 61 patients). Informed consent was taken from all patients and controls before ethical committee approval was obtained.

Glomerular filtration rate (eGFR) was estimated using the abbreviated Modification of Diet in Renal Disease (MDRD) Study equation[15]. The stages of CKD were defined according to the American National Kidney Foundation: Stage IV, eGFR 15-29 (n=31) and stage V, eGFR <15 mL/min/1.73m^2 (n=30). Patients were divided into two groups according to the mean Hb level: 31 patients had blood level of Hb below 10.3 g/dL (subgroup A) and 30 patients above 10.3 g/dL (subgroup B).

All participants underwent a comprehensive physical examination, laboratory investigations and echocardiography. In addition, all subjects completed a questionnaire on demographic parameters, medical history and current medication. Venous blood samples were collected in the morning immediately before echocardiographic investigation after overnight fasting. Standard laboratory analyses were measured using routine laboratory methods. The level of intact parathyroid hormone (iPTH) was determined by radioimmunoassay (RIA) method. High sensitivity C-reactive protein (hsCRP) was measured using a latex-enhanced immunoturbidimetric method on an Olympus AU400 biochemistry analyzer. NT-proBNP was measured with Cardiac Reader, a commercially available point-of-care equipment (Roche Diagnostics GmbH, Mannheim, Germany). Using the principle of immunochromatography, this test measures concentrations of NT-proBNP from 60 to 3000 pg/mL[16].

Echocardiography was performed using a Toshiba Power Vision 6000 equipped with a multi-frequency (2.5-5.0 MHz), phased array transducer by the same experienced observer who was unaware of the clinical data. From two-dimensional guided M-mode echocardiography, left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter (LVESD), interventricular septal thickness in diastole (IVSTd), left ventricular posterior thickness in diastole (PWTd) and left atrial (LA) diameter were measured. LV mass was calculated according to the Devereux formula and divided by body surface area to obtain LV mass index (LVMI). Presence of LV hypertrophy (LVH) was defined as LVMI greater than 115 g/m^2 for men and 95 g/m^2 for women[17]. Left ventricular ejection fraction (LVEF) was calculated using modified Simpson's rule, and fractional shortening (LVFS) was calculated from the reduction of LV internal diameter during the cardiac cycle. Mitral inflow velocities were recorded using pulsed wave Doppler as: transmitral peak early diastolic velocity (E), transmitral peak late diastolic velocity (A) and the proportion of these two variables (E/A). In addition, the deceleration time of the early diastolic wave (DT), the isovolumetric relaxation time (IVRT) and color Doppler M-mode flow propagation velocity (Vp) were measured. Tissue Doppler imaging (TDI) was applied in the pulse-Doppler mode to record the mitral annular velocities at the septal and lateral corners. Myocardial tissue velocities were measured in early diastole (E′) and late diastole (A′), and the E'/A' ratio were calculated at both corners of the mitral annulus. To estimate the LV filling pressure, the ratio of early transmitral flow velocity (E) to early diastolic mitral annular velocity (E/E') was calculated.

Continuous data were expressed as mean ± SD or median (interquartile rang, IQR) and categorical data as percentages. Differences between two groups were compared by Student's t-test and Mann-Whitney U test for continuous variables and χ^2 test for categorical variables. One-way ANOVA followed by post hoc test was used to determine the difference between control group and two subgroups of CKD patients. The relationship between two continuous variables was assessed by a bivariate correlation method (Pearson's correlation). Because NT-proBNP values were not normally distributed, a natural logarithmic transformation was used. Multivariable linear regression analysis was used to clarify the contribution of each independent variable to NT-proBNP having lnNT-proBNP as the dependent variable. All variables with univariable association significant at the $p<0.05$ level were selected for backward multivariable analysis. Data analysis was performed using SPSS version 16 (Statistical Package for Social Sciences for Windows, SPSS Inc., Chicago, IL). Statistical

significance was assumed at p<0.05.

Results

Baseline characteristics of CKD patients and control subjects are listed in Table 1, while the values of NT-proBNP are shown in Table 2. The mean values of hemoglobin and hematocrit (Htc) were significantly lower (p<0.001), and the mean value of NT-proBNP was significantly higher (p<0.001) in patients with CKD than in controls. Patients with more severe anemia (subgroup A) were older (p<0.001) and had lower values of serum albumin (p<0.01), compared with subgroup B. There were no significant differences between the tested subgroups with respect to gender, BMI and blood pressure level. As expected, the mean values of urea and creatinine were significantly higher (p<0.01 and p<0.001, respectively), and the value of eGFR was significantly lower (p<0.01) in the subgroup of patients with a greater degree of renal anemia. Mean value of NT-proBNP in patients from the subgroup A was significantly higher compared to patients from subgroup B (median: 1507.0 vs 441.5 pg/mL, p<0.001).

The comparisons of conventional and TDI echocardiographic parameters in patients and controls are presented in Table 2. Echocardiography showed a significant increase of LA diameter (p=0.001), PWTd (p<0.01) and IVSTd (p<0.001) in subgroup A compared with subgroup B. Patients from subgroup A had also significantly higher LV mass (p<0.001) and LVMI (p<0.001), and higher prevalence of LVH (100% vs 83.3%; p<0.05) than patients from subgroup B. There was no significant difference between groups in regard to systolic and diastolic function, as measured by means of the conventional echocardiographic parameters LVEF and LVFS, and Doppler derived E/A, DT and IVRT. Nevertheless, color M-mode flow propagation velocity was significantly lower in subgroup A than in subgroup B (Vp: 36.0±7.6 vs 43.4±10.1, p<0.01). When the mean values of TDI parameters of two subgroups were compared, lateral E' velocity, septal E'/A' and lateral E'/A' ratio were significantly decreased in patients with more severe anemia, which was consistent with the altered diastolic filling of the LV in this subgroup.

The natural logarithms of NT-proBNP levels showed significant negative correlations with Hb and Htc in univariant regression analysis (p<0.001). The inverse relationship between lnNT-proBNP and Hb level in CKD patients was

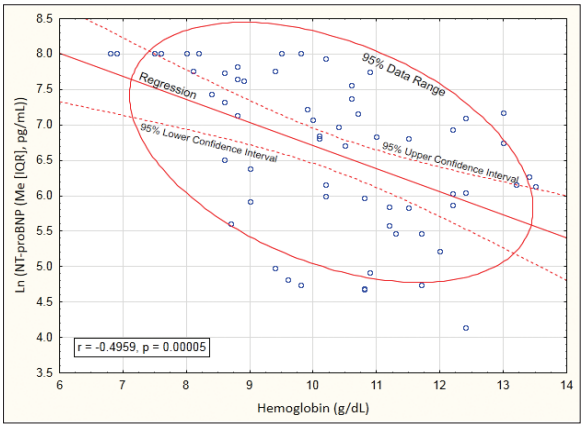

Figure 1: Relationship between lnNT-proBNP and Hb level in patients with chronic kidney disease.

Table 1: Baseline characteristics of patients with chronic kidney disease (stage IV-V) and control subjects.

Variable	Patients, all	**Subgroup A**	**Subgroup B**	Controls	p
Age (years)	62.6±13.6	70.1±9.3#*	55.0±13.1*	63.7±9.0	0.000
Gender (male/female)	34/27	15/16	19/11	12/10	0.345
BMI (kg/m^2)	26.1±5.3	25.0±5.0	27.2±5.5	26.0±3.5	0.220
Systolic BP (mmHg)	139.9±20.2	144.3±20.1	135.3±19.6	138.4±11.9	0.150
Diastolic BP(mmHg)	83.6±11.1	84.7±11.8	82.5±10.4	83.4±5.2	0.691
Hemoglobin (g/dL)	10.3±1.7*	8.9±1.0#*	11.7±9.4*	13.9±1.2	0.000
Hematocrit (%)	28.7±5.1*	24.6±2.8#*	32.9±3.1*	38.6±4.5	0.000
Albumin (g/L)	39.0±6.3	36.8±5.5#*	41.3±6.2	39.9±3.6	0.006
Fibrinogen (g/L)	4.0±1.2*	3.8±1.1*	4.1±1.4*	3.1±0.9	0.011
Creatinine (μmol/L)	355.0±112.4*	391.7±127.3#*	317.0±80.3*	74.4±16.1	0.000
Urea (mmol/L)	18.5±5.5*	20.9±5.6#*	16.1±4.4*	6.1±2.0	0.000
Cholesterol (mmol/L)	5.5±1.4	5.4±1.3	5.6±1.6	5.4±1.1	0.872
Triglycerides (mmol/L)	2.1±1.3*	2.2±1.2*	2.0±1.3	1.4±0.9	0.054
Potassium (mmol/L)	5.3±0.8*	5.4±0.8*	5.3±0.7*	4.1±0.5	0.000
Calcium (mmol/L)	2.4±0.2*	2.4±1.8*	2.3±1.4*	2.5±0.2	0.003
Phosphorus (mmol/L)	1.3±0.3*	1.3±0.3*	1.3±0.3*	1.0±0.2	0.000
iPTH (Me [IQR], pg/mL)	138.8 (604.0) *	138.8 (155.2)*	139.6 (214.1)*	28.3 (36.6)	0.000
hsCRP (Me [IQR], mg/L)	2.6 (9.4) *	3.5 (12.4)	2.5 (5.1)	1.8 (2.2)	0.119
eGFR (mL/min/1.73m^2)	15.8±5.7*	13.5±4.6#*	18.2±5.8*	89.0±18.6	0.000

p: statistically significant difference between groups (A, B and controls), BMI: body mass index, BP: blood pressure, iPTH: intact parathyroid hormone, Me [IQR]: Median [interquartile rang], hsCRP: high-sensitivity C-reactive protein, eGFR: estimated glomerular filtration rate, *statistically significant difference compared to controls (p<0.05), #statistically significant difference compared to subgroup B (p<0.05).

Table 2: NT-proBNP and echocardiographic parameters of patients with chronic kidney disease (stage IV-V) and control subjects.

Variable	Patients, all	**Subgroup A**	**Subgroup B**	Controls	p
NT-proBNP (Me [IQR], pg/mL)	905.0 (1565.0)*	1507.0 (2368.0)#*	441.5 (804.0)*	114.5 (647.0)	0.000
M-mode and 2-D measurements					
LA diameter (mm)	43.8±4.9*	45.8±4.1#*	41.7±4.8	40.5±4.4	0.000
PWTd (mm)	11.0±1.3*	11.4±1.0#*	10.4±1.3*	9.4±1.2	0.000
IVSTd (mm)	11.9±1.5*	12.6±1.4#*	11.2±1.3*	10.5±6.9	0.000
LVEDD(mm)	51.5±5.5	52.3±0.53	50.5±5.7	51.2±4.9	0.423
LVESD (mm)	33.9±4.9	34.6±5.6	33.1±4.0	33.9±4.9	0.489
LV mass (g)	298.2±79.7*	331.5±78.5#*	263.7±66.0	239.0±56.8	0.000
LVMI (g/m^2)	170.0±48.9*	196.5±49.4#*	142,5±29.8	129.7±24.1	0.000
LVH, prevalence (%)	91.8*	100#*	83.3	68.2	0.005
LV ejection fraction (%)	61.7±8.2	61.1±9.2	62.2±7.1	61.6±6.8	0.860
LV fractional shortening (%)	34.1±5.6	33.5±6.4	34.6±4.7	34.0±5.6	0.740
Mitral inflow velocities					
E/A ratio	0.8±0.3	0.8±0.2	0.9±0.3	0.9±0.3#	0.120
DT (ms)	241.2±63.5	231.1±61.7	250.9±64.7	254.6±69.1	0.362
IVRT (ms)	86.9±29.0	86.9±29.7	87.0±28.7	88.2±18.2	0.982
Vp (ms)	39.6±9.6*	36.0±7.6#*	43.3±10.1	46.3±9.77	0.000
Tissues Doppler Imaging					
Septal E' (cm/s)	7.3±1.9*	7.0±2,0*	7.7±1.9*	9.6±2.0	0.000
Septal A' (cm/s)	11.5±3.0*	11.9±3.2*	11.2±2.8*	14.1±2.8	0.002
Septal E'/A' ratio	0.7±0.2	0.6±0.2#	0.7±0.2	0.7±0.2	0.05
Lateral E' (cm/s)	10.0±3.0*	9.2±2.5#*	10.9±3.3	11.6±2.4	0.007
Lateral A' (cm/s)	13.1±3.6	13.3±3.4	12.9±3.8	14.6±3.7	0.220
Lateral E'/A' ratio	0.8±0.3	0.7±0.1#	0.8±0.2	0.8±0.3	0.039
LV diastolic filling pressure					
Septal E/E' ratio	9.1±3.9*	9.7±4.6*	8.4±2.9*	5.8±1.9	0.001
Lateral E/E' ratio	6.8±3.0*	7.4±3.6*	6.1±2.2	4.8±1.5	0.003

p: statistically significant difference between groups (A, B and controls), NT-proBNP: N-terminal pro B type natriuretic peptide, Me [IQR]: Median [interquartile rang], LA: left atrial, PWTd: posterior wall thickness in diastole, IVSTd: interventricular septal thickness in diastole, LVEDD: left ventricular end-diastolic diameter, LVESD: left ventricular end-systolic diameter, LVH: left ventricular hypertrophy, E/A: ratio of early-to-late transmitral flow velocity, DT: deceleration time, IVRT: isovolumetric relaxation time, Vp: mitral flow propagation velocity, E': early diastolic mitral annular velocity, A': late diastolic mitral annular velocity, *statistically significant difference compared to controls ($p<0.05$), #statistically significant difference compared to subgroup B ($p<0.05$).

Table 3: Univariable and multivariable predictors of lnNT-proBNP as the dependent variable.

Variable	**Univariable analysis**		**Multivariable analysis**	
	r	p-value	St. Beta	p-value
Age	0.425	0.001	-	-
Hemoglobin	-0.496	<0.001	-0.324	0.002
Hematocrit	-0.491	<0.001	-	-
Cholesterol	-0.318	0.012	-0.402	<0.001
LDL cholesterol	-0.344	0.007	-	-
eGFR	-0.270	0.035	-	-
LA diameter	0.302	0.018	0.189	0.061
LVMI	0.306	0.016	-	-
LVEF	-0.286	0.025	-0.369	<0.001
LVFS	-0.271	0.034	-	-
Septal E/E' ratio	0.287	0.025	-0,298	0.003
Lateral E/E' ratio	0.336	0.008	-	-

LDL: low density lipoprotein, eGFR: estimated glomerular filtration rate, LA: left atrial, LVMI: left ventricular mass index, LVEF: left ventricular ejection fraction, LVFS: left ventricular fraction shortening, E/E': early mitral inflow velocity to early diastolic mitral annular velocity ratio. For univariable analysis, the Pearson correlation (r) and p-value are shown. For the multivariable analysis, the standardized coefficient Beta and p-value are shown.

shown in Figure 1. Additionally, lnNT-proBNP levels correlated significantly with age, cholesterol, LDL-cholesterol, eGFR, LA diameter, LVMI, LVEF, LVFS, septal E/E' and lateral E/E' ratio. Multivariant linear regression analysis, backward method, revealed lnNT-proBNP levels to be dependently related to Hb, cholesterol, LA diameter, LVEF and septal E/E' ratio, according to the following equation: lnNT-proBNP = 10.929 – 0.021*Hb – 0.307*cholesterol + 0.423*LA diameter – 0.049*LVEF + 0.083*septal E/E'. The correlation between original value of lnNT-proBNP and calculated using given equation was r=0.733; p<0.001 (Table 3).

Discussion

Cardiovascular disease is the leading cause of morbidity and mortality in the patients with end-stage renal disease, accounting for more than 50% of all deaths[18]. An excessive cardiovascular risk among these patients related to a very high incidence of cardiac hypertrophy, cardiomyopathy, heart failure, and coronary artery disease. Echocardiography is recommended as a fundamental tool for profiling cardiovascular disease in CKD patients. It is also considered that both BNP and NT-proBNP may play

an adjunctive role to echocardiography as additional tools to early identify CKD patients who are at a heightened cardiovascular risk. Non-cardiac determinants that may influence BNP (NT-proBNP) levels include advancing age, gender, obesity, renal function and presence of anemia. The present study was designed to evaluate the interrelationship of anemia, the degree of renal failure and echocardiographic abnormalities, as well as their impact on the level of NT-proBNP in asymptomatic patients with advanced CKD.

Our results revealed advanced age and lower values of serum albumin in CKD patients with a greater degree of anemia (subgroup A) compared with subgroup B. It has already been documented that serum albumin decreases with advancing age in patients with normal renal function as well as in patients with CKD[19]. Hypoalbuminemia is the most commonly used surrogate of protein-energy malnutrition in patients with CKD and has a strong association with increased cardiovascular morbidity and mortality[20]. A confounding factor is that serum albumin is also a negative acute phase reactant and its serum level is profoundly affected by the presence of an inflammatory response. The recent concept is that nutrition and inflammation may be linked in accelerating the cardiovascular disease in patients with CKD[21]. However, in our study there were no significant differences regarding the other inflammatory markers (fibrinogen, hsCRP) between two subgroups of CKD patients. On the other hand, we have recorded a lower average BMI in subgroup A, although not statistically significant. In addition, the level of urea and creatinine was significantly higher, and the value of eGFR was significantly lower in subgroup of patients with lower Hb, indicating a relation between the degree of anemia and level of kidney function.

At the same time it has been confirmed that CKD patients with lower Hb values have significantly higher values of NT-proBNP. The close association between lower Hb levels and elevated values of NT-proBNP, as a marker of hemodynamic stress, might be explained by the several mechanisms. Hemodynamic mechanisms of adaptation to chronic anemia include increased cardiac output mediated by lower after-load, elevated pre-load and increased LV function attributed to increased sympathetic nervous system activity. The reduction in after-load occurs as a result of decrease in systemic vascular resistance due to reduced blood viscosity and hypoxia-induced vasodilation. The increase in pre-load occurs as a result of increased venous return, which is partly consequence of the retention of water and salt due to activation of the renin-angiotensin-aldosterone system[3]. It means that the state of chronic anemia results in elevated plasma volume, and BNP and NT-proBNP may be released in response to ventricular plasma overload and increased wall stress[22]. Furthermore, in the presence of anemia the production of these vasodilatory peptides may be increased to counteract the vasoconstrictive effects of the circulating neurohormones such as catecholamines and angiotensin II. In accordance with this hypothesis, studies have shown that a varety of vasoconstrictive neurohormones, including norepinephrine and angiotensin II, directly stimulate the production of natriuretic peptides[23].

The results of our study also confirm the relationship between the degree of anemia and the alterations in cardiac structure and function. Patients with hemoglobin levels below 10.3 g/dL had significantly greater LVMI and higher prevalence of LVH. Chronic anemia is known to result in increased venous return and increased cardiac work which may lead to LVH and subsequent cardiac enlargement. Over time functional changes occur, with impaired LV ventricular relaxation and compliance[3]. Indeed, lower values of echocardiographic parameters of diastolic function Vp, E', and E'/A' ratio in our patients with more severe anemia are in accordance with these pathophysiological changes. In the presence LVH and anemia, there is also a reduction in the level of coronary vasodilator reserve below that needed to meet cardiac oxygen demands, resulting in myocardial ischemia[24]. An ischemic heart is more sensitive than a normal heart to even smaller drops in hemoglobin, yielding worsening of cardiac function[25]. It is possible that level of NT-proBNP is the result of subclinical ventricular dysfunction and in this case, low Hb may reflect hemodilution in the context of volume overload rather than true anemia[26].

In univariate correlation analysis, we found that lnNT-proBNP in CKD patients was negatively associated with Hb, Htc, eGFR, cholesterol, LDL cholesterol, LVEF and LVFS, but positively correlated with age, LA diameter, LVMI and ratio E/E' (Table 3). Given the limitation of univariate analysis in differentiating confounding factors, multiple backward regression analysis was further performed by including all these possible factors as independent variables. The regression analysis identified that total cholesterol, Hb, LVEF and septal E/E' ratio were independent determinants of lnNT-proBNP in our patients. These factors could explain about 54% of variation in lnNT-proBNP (R Square=0.537). An inverse relationship between serum NT-proBNP and cholesterol has been described previously and has been hypothesized to be a potential link impairing the natural blood pressure regulation[27]. It appears that this relationship between anemia and NTproBNP is independent of renal function. This is consistent with recent findings that renal NT-proBNP extraction was sustained and/or enhanced in the presence of moderate kidney dysfunction, suggesting that rising levels of NT-proBNP in kidney disease is not caused by impaired renal clearance[28]. Thus, elevated levels of NT-proBNP in CKD patients could be explained by the combined effect of renal anemia and abnormalities of cardiac function that develop progressively with decline in renal function. In line with our observation, a study of Dong SJ et al showed that plasma NT-proBNP levels were significantly higher in clinically stable, ambulatory cohort of cardiac patients with LV systolic dysfunction and/or elevated filling pressures, independent of the effects of LV mass, renal function and age[29].

Our results indicate that degree of anaemia should be taken into account when interpreting elevated levels of NT-proBNP in asymptomatic CKD patients. Brucks et al showed that anemia in diastolic heart failure associated with greater elevations in serum BNP level, more severe diastolic dysfunction and a worse prognosis[11]. In a group

of 809 patients with coronary heart disease and no history of heart failure, anemia remained independently associated with NT-proBNP even after adjustment for cardiovascular risk factors[12]. A study by Knudsen et al also suggest that anemia may contribute to the increase of BNP level in the absence of heart failure, and that anemia may complicate the interpretation of the relationship between BNP and cardiac function, as well as prognosis[13]. A smaller number of studies considered anemia as a predictor of levels of natriuretic peptides in CKD patients. Thus, Mark et al showed in a cross-sectional study of 296 patients with different stages of CKD that serum BNP levels were significantly confounded by numerous non-cardiac factors, including beta blockade, albumin, hemoglobin, age and renal function[14].

In conclusion, the increased NT-proBNP levels in asymptomatic patients with CKD were independently associated with echocardiographic parameters of LV dysfunction, but anemia may represent one of the important confounder of the relationship between NT-proBNP and cardiovascular abnormalities. Therefore, the presence and degree of anemia may be of clinical importance when interpreting the results of NT-proBNP measurements for the detection of LV dysfunction and the prediction of adverse clinical outcomes. Further studies are needed to assess the impact of the correction of hemoglobin on circulating levels of NT-proBNP in predialysis CKD patients.

Disclosure

The authors have no conflict of interest.

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